Medicinal Cannabis for Post-Traumatic Stress Disorder:
Efficacy of Whole-Plant Vaporization based on Cannabinoid Concentration

A Research Proposal for D&B Wellness

and

The State of Connecticut Department of Health

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Rationale and Background

As the medicinal marijuana program in Connecticut progresses and producers begin to provide an increased range of products available to our patients, we will begin research that focuses in depth on the therapeutic efficacy of these products in relation to their cannabinoid and terpene profiles. Cannabis contains a wide variety of pharmaceutical compounds that seem to work synergistically together, but as technology and methods of production increase, patients begin to be presented with marijuana products that focus specifically on a higher concentration of certain compounds called cannabinoids. It has been suggested by researchers that these compounds "deserve further attention regarding their contributions to the effects of clinical cannabis" (Russo, 2001).

FIGURE 1
Chemical Structure of Cannabidiol
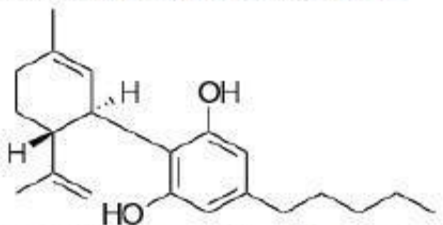
2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol

FIGURE 2
Chemical Structure of Δ⁹-Tetrahydrocannabinol
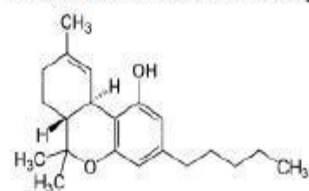
(−)-(6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol

The cannabis plant, in all its biotypes, contain compounds known as "phytocannabinoids" that are defined as the C_{21} terpenphenolic compounds naturally occuring in the cannabis plant (to distinguish from endogenous cannabinoids and synthetic cannabinoids). While these compounds are not solely responsible for the therapeutic effects of cannabis, they have been those which have seen the most attention; two in particular having certain scientific promise. Cannabidiol (CBD, *fig. 1*) is a non-psychoactive cannabinoid that, as the naturally

occurring (-) enantiomer, acts as a CB_2 receptor inverse agonist. CBD occurs either It has been reported by clinical trials to have neuroprotective, anti-inflammatory, antipsychotic and sedative/hypnotic effects. Research on both animals and humans has supported the anxiolytic effect of CBD and reported its administration being relatively well tolerated (Mechoulam et. al, 2002) A 2012 review of the current scientific literature regarding CBD concluded that it is "the cannabinoid compound that is closer to have its preliminary findings in anxiety translated into clinical practice", and that "future studies should test this possibility in clinical trials involving patients with anxiety disorders" (Schier et. al). Tetrahydrocannibinol (figure two) is the main psychoactive component of cannabis. It is the most widely researched and well understood phytocannabinoid and has been approved by the FDA for the treatment of anorexia in AIDS patients and refractory nausea and vomiting in patients undergoing chemotherapy. Clinical research has found THC both alone, in combination with CBD and as cannabis to be an effective therapeutic for a large number of illnesses and symptoms (Kumar et. al, 2001).

Post-traumatic stress disorder (PTSD) is an anxiety disorder that occurs after being exposed to significant and devastating emotional trauma, causing unpleasant symptoms long after the trauma occurs. Despite advances in psychotherapeutic approaches and novel treatments (e.g. eye movement desensitization and reprocessing), PTSD has proven a condition with a high probability for treatment resistance and recurrence. PTSD commonly presents clinically with comorbid psychiatric conditions, making evaluating treatment efficacy in PTSD alone challenging. It is suggested that 80% of patients diagnosed with PTSD also qualify for at least one other mental disorder as classified by the DSM-IV-TR. The most common of these comorbidities are major depressive disorder, substance abuse disorder or another anxiety disorder besides PTSD (Kessler et. al, 2005). The primary goals of PTSD

pharmacotherapy are the alleviation of core symptom severity, improvement of psychosocial functioning, increasing resilience and improvement of ability to cope with stressors (Hidalgo & Davidson, 2000). Neurobiological changes are found in patients diagnosed with PTSD, including altered neuroanatomy of the prefrontal cortex and limbic system. One theoretical model proposes that drugs which interact strongly with memory processes might prevent the development of the disorder if administered during the acute manifestation (O'Brien & Nutt, 1998). It has been demonstrated in the rat models of PTSD that a dysfunction of pattern completion and separation in hippocampal nervous conduction through the dentae gyrus, CA1 and CA3. Interrupting the long-term potentiation (LTP) between neurons in this area, which contributes to the inappropriate and pathological pattern completion observed in PTSD, may be key to some of the most severe behavioral manifestions of the disease. Both CBD and THC have been shown to interact with the brain's memory processing functions. THC has been found to have reversible disruptive effects on hippocampal LTP and working memory in humans through modulation of CB1 receptors in the hippocampus (Wise et. al, 2009).

Recent studies examining cannabinoids and PTSD using animal stress models and the pavlovian conditioning paradigm, which is to say the response of fear and hypervigilance to stress long after circumstances no longer necessitate such a dramatic reaction is a learned and conditioned response, have found CB1 agonists to have a positive effect on long term extinction and reducing fear response (de Bitencort et. al, 2013; Reich et. al, 2013). Furthermore, it was discovered that the endocannabinoid system was downregulated by chronic mild stress in rodents (Reich et. al, 2013). Research done on healthy human subjects has revealed THC facilitated fear extinction through modulation of the prefrontal-limbic circuits and concluded "the cannabinoid system may serve as a promising target for innovative

intervention strategies (e.g. pharmacological enhancement of exposure-based therapy) in PTSD" (Rabinak et. al, 2013). Persistent nightmares experienced by PTSD patients were found to be alleviated by the synthetic cannabinoid nabilone (Fraser et. al, 2009). The brain's endocannabinoid system displays increased cannabinoid receptor availability and decreased levels of the endogenous cannabinoid neurotransmitter anandamide, a possible explanation for the therapeutic benefits of cannabinoid receptor agonists in PTSD (Neumeister et. al, 2013).

Proponents of phytomedicine have argued the gestalt approach to whole-plant medication; that the therapeutic value of a botanical medicine is more than the sum of its constituent parts. The cannabis plant contains more than 400 different compounds, a significant number of which have unique pharmacological action. Eighteen different classes of chemicals, including nitrogenous compounds, amino acids, hydrocarbons, carbohydrates, terpenes, and simple and fatty acids, contribute to the known pharmacological and toxicological properties of cannabis. Non-cannabinoids present in cannabis have distinct therapeutic value, for example, the terpenoids linalool, cinronellol and alpha-terpineol present in cannabis were all found to have discernable sedative and anxiolytic effects (Buchbauer et al., 1993). Many cannabinoid compounds are closely related or direct products of one another, yet still retain unique and clinically significant effects separate from their counterparts. Mc Partland and Russo (2001) outline the benefits of whole plant cannabis based medicine from synergy between compounds as well as the mitigation of side effects through interaction, for example, the reduction of THC's unwanted psychoactive side effects (i.e., anxiogenesis, paranoia, audiovisual hallucinations) by cocommitent CBD ingestion. Pharmacokinetic alterations result in intricate processes of potentiation and mitigation to

specific drug effects, a phenomena deemed the "entourage effect", which is best illustrated by the model of phytocannabinoid-terpenoid synergy proposed by Russo (2011). These findings emphasize the importance of whole plant cannabis research, rather than research on preparations like nabiximols or marinol which synthetically isolate one or two cannabinoids.

The aim of this study will be to evaluate the efficacy and tolerability of treatment with high CBD/low THC (herein high CBD) medicinal cannabis, high THC/low CBD (herein high THC) medicinal cannabis and placebo (as well as in comparison with each other) in adult patients with a primary diagnosis of post-traumatic stress disorder as defined by the Diagnostic and Statistics Manual of Mental Disorders, fourth edition text revision (DSM-IV-TR, table 1). A flexible-dose range double-blind placebo-controlled randomised clinical trial will be conducted to determine the range of therapeutic differences, if any, which exist between treatment with these marijuana products.

Research &
Development

Table 1. DSM-IV-TR Criteria for PTSD

Criterion A: A traumatic event in which

1. The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others.

2. The person's response involved intense fear, helplessness, or horror.

Criterion B: intrusive recollection (at least 1)

1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions

2. Recurrent distressing dreams of the event

3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated)

4. Intense psychological distress at exposure to internal or external trauma-related cues

5. Physiologic reactivity upon exposure to internal or external trauma-related cues

Criterion C: avoidant/numbing (at least 3, not present before the trauma)

1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma

2. Efforts to avoid activities, places, or people that arouse recollections of the trauma

3. Inability to recall an important aspect of the trauma

4. Markedly diminished interest or participation in significant activities

5. Feeling of detachment or estrangement from others

6. Restricted range of affect (e.g., unable to have loving feelings)

7. Sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal lifespan)

Criterion D: hyperarousal (at least 2, not present before the trauma)

1. Difficulty falling or staying asleep

2. Irritability or outbursts of anger

3. Difficulty concentrating

4. Hypervigilance

5. Exaggerated startle response

Criterion E: Duration of the disturbance (symptoms in B, C, and D) is more than one month.

Criterion F: The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Acute: if duration of symptoms is less than 3 months

Chronic: if duration of symptoms is 3 months or more

Adapted, with permission, from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision. Washington, DC, American Psychiatric Association, 2000.

Sample Selection and Screening

The study aims to enroll subjects of both genders into a 12-week long trial. Each subject will provide written consent. Participants will be informed of: their rights as patients enrolled as human subjects in medical research including their right to privacy as afforded to them by the

Health Insurance Portability and Accountability Act (HIPAA) and guaranteed anonymity and confidentiality as far as it can feasibly be preserved, their rights as medicinal marijuana patients registered in the state of Connecticut, the scope of the study, their status as volunteers, and provided a full written and oral explanation of research safety protocols, compliance with the treatment program, benefits and risks associated with participation in the study and the medication provided thereby. Patients who enter research are to be referred by local clinicians and/or a Connecticut state dispensary. The patient population will consist of subjects with symptomatic PTSD status post service in the armed forces ("veterans"). The prevalence of PTSD in this population, according to a RAND meta-analysis of current literature titled *Invisible Wounds of War*, reports a rate of "roughly 5 to 15 percent of service members, depending on who is assessed and when they are assessed" (Greenberg, 2009; Holdeman, 2009).

Prospective participants may have been the recipient of information detailing a research study involving veterans diagnosed with PTSD who qualify as medicinal marijuana patients in the state of Connecticut, whether they are currently using medicinal marijuana or not, and who are experiencing post-traumatic stress and associated symptoms refractory to past and current interventions. Advertisements may be utilized, with explicit written permission, at practices and treatment centers amicable to involvement.

Patients' voluntary agreement to participate in the study will include an offer of compensation based on time spent directly involved, as well as for transportation costs. Participants may apply to be screened for eligibility via e-mail or on site at the testing facility. Participants will be informed of their rights as patients enrolled as human subjects in medical research including their right to privacy as afforded to them by the Health Insurance Portability and

Accountability Act (HIPAA) and guaranteed anonymity and confidentiality as far as it can feasibly be preserved, their rights as medicinal marijuana patients registered in the state of Connecticut, the scope of the study, their status as volunteers, and provided a full written and oral explanation of research safety protocols, compliance with the treatment program, benefits and risks associated with the study and procedures. Necessary approval and written consent will be obtained from all participants in the study. To meet eligibility requirements, patients must be aged 18-60 years old, have a primary diagnosis of post-traumatic stress disorder secondary to military service for more than one month, subjectively describe their current symptoms as resistant to attempted treatment modalities to date and currently participating in a psychotherapeutic program meeting at least once a week. To further ensure privacy and confidentiality, after the confirmation is completed participant names will be discarded in favor of an identification number associated only with their individual data. Exclusion criteria will include:

- Past medical history or current diagnosis of psychosis, suicidal ideation, substance abuse disorder, malingering, organic neurological disorder or other mental disorder[1], significant cardiovascular disease, or significant hypertension

- Prescription drugs that metabolize exclusively via cytochrome P450 3A4 enzymatic process

- Substance or alcohol abuse or dependency within the past six months, including recreational cannabis

- Pregnancy, lactation or current attempts to become pregnant

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[1] Due to the often inseparable nature of comorbid disorders in post-traumatic stress, patients who have been diagnosed with certain psychiatric comorbidities (i.e. generalized anxiety disorder, adjustment disorder, dysthymia, major depressive disorder) under control for more than six months may be considered pending clinical evaluation.

- Intolerance to the effects of psychoactive drugs (subjective)

Each patient, or their referring physician, will be encouraged to provide a detailed medical and psychiatric history, as well as their current valid medicinal marijuana recommendation and registration with the state of Connecticut, for cross reference against exclusion criteria. At admission, all patients will undergo a clinical evaluation consisting of:

- A comprehensive Review of Systems (ROS):

    - Head-to-Toe Physical Examination

    - Recorded Vital Signs (HR, RR, BP, SpO2, Temperature)

    - If deemed necessary, routine diagnostics (e.g., BMP, CBC, 12-Lead EKG)

- 12-Panel Urinalysis

- Initial Screening Scales:

    - CGI-S

    - PCL-M

    - SPRINT

- Administration of subtherapeutic dose of medicinal cannabis (allergy test)

After the clinical evaluation, patients will be excluded based on the following:

- Positive result for illicit drugs

- Baseline PCL-M score of below 50

- SPRINT invalidation of PTSD diagnosis

- Sustained tachycardia, impaired respiratory function and/or unresolved abnormal exam findings of concern

Those remaining participants will be our sample population. Participants will be compensated for their time at the end of the study, for an amount tentative on the time spent directly

involved. Patients will be counselled on the use of medicinal cannabis and the side effects that may be associated with its use and advised to have someone with them when they first administer the drug, and until they are used to the effects. Patients will be warned about the possibly intoxicating effects of cannabis and instructed not to drive or operate heavy machinery while under its effect. Patients will be informed on the potential for addiction and habituation, introduced to resources they may utilize if they feel they have a problem and advised that they significantly reduce their risk for addiction if they use medicinal cannabis appropriately as prescribed- as is the case with all other medically useful but potentially addictive drugs. It will be emphasized that each patient should follow the recommendations of their personal physician and psychiatrist during the course of the study, and it will be requested that any changes in medications or master treatment plans be reported to the researchers as soon as possible. Any patient who meets exclusion criteria while the study is underway will be asked to discontinue all interventions, be debriefed and have their relevant data destroyed.

Titration

All patients will perform titration under the supervision of the researchers and markers for cannabis activity (tachycardia, postural hypotension, subjective reports of intoxication) will be observed by researchers as patients titrate their dose until they have reached symptom relief. A dosing schedule of 25 milligrams (.025g) of vaporized cannabis inhaled every 15 minutes, with a report on the subjective effects after every administration. Inhalation results in a very rapid onset of effects. A comprehensive pharmacokinetic study by Huertis in 2009 recorded

the mean time to peak plasma concentration following inhaled cannabis to be 13.5 minutes, as measured by serological concentration of the THC metabolite 11-OH-THC. The dosing will be repeated q15m until either symptom alleviation is reported or side effects become substantial. Patients will be instructed to use 50-75% of the total dose required to reach optimal clinical benefit as their first "at-home" dose, and re-titrate themselves. Patients will be instructed to reduce their dose to the previous level if side effects such as excessive sedation, paranoia or confusion appear. For patients who exhibit sensitivity to the effects of marijuana, the dosage increment will be reduced to .0125g of vaporized cannabis to allow for increased control of effects.

Study Design

A series of double-blind, randomised, placebo-controlled single patient crossover ("n-of-one" design) with a treatment period of 12 weeks will be performed in this study (Guyatt et. al, 1990). In this design, each patient will act as his or her own control. This design is optimal for this first study for a number of reasons, including that "n-of-one" studies generate information on the efficacy of the treatment with a more individualized approach that each patient will be able to use to tailor their treatment plan after the study is completed, while still retaining the rigorous nature of the double-blind, placebo-controlled crossover. Also, new information from each individual patient will alert the researchers quickly if any modifications need to be made to the study design. Further rationale for this design rather than a parallel group assignment is found in the Institute of Medicine's 1999 support for the single-patient crossover design, which reads:

The challenge of integrating the ideal of standardized and rigorous processes for treatment evaluation with everyday clinical practice has encouraged interest in single-patient trials. Methods for such trials have been established and tested in a variety of clinical settings, usually under everyday conditions. They are particularly valuable when physicians or patients are uncertain about the efficacy of treatment for symptomatic diseases. Controls can be incorporated even in this kind of trial. Such trials can be double blinded and can involve cross-over designs in which the patient is treated with alternating treatments, such as placebo-drug-placebo or one drug followed by another drug. As with any other clinical trial, a single-patient trial should be designed to permit objective comparison between treatments.

This design will also ensure that the sliding scale of dosage, as determined by titration against symptom relief or adverse side effects, does not present a confounding variable to analysis within parallel groups and allows for a greater degree of freedom and flexibility when working with this very sensitive patient population.

Treatment Period and Data Collection

On a week to week basis, patients will self-administer either high CBD medicinal marijuana, high THC medicinal marijuana or placebo for twelve weeks. Patients will be randomly assigned to a three-week structure consisting of two weeks of each high-THC, placebo, high-CBD. The first period will proceed as placebo-high CBD-high THC-placebo-high THC-high CBD. In this manner, we record a period of placebo with no treatment exposure and

each form of medicinal cannabis will directly follow a period of placebo to mediate the potential for tolerance development interferring between treatments. Patients will be blind to the schedule, but instructed that there will be three different kinds of medication utilized in the study. Further research is necessary to determine if alterations to the scent and taste of the placebo will be necessary to preserve the effect's integrity. Patients will keep a diary in which they will record symptom , functioning and subjective intoxication scores daily. Every two weeks, clinic visits will occur when a psychiatrist will assess, double-blind, the patient's CGI score, a GAF score, a PCL-M score, record reports of adverse drug effects and collect urinalysis which will be analysed for cannabinoid content using a homogenous enzyme immunoassay (EMIT) as described by DeLaurentis et. al (1982).

Termination

At the end of the study, it will be considered, for ethical reasons, offering the patients who took part in the study an option to continue receiving medicinal marijuana from D&B Wellness in a research capacity. In addition to providing a service to patients who experienced relief, this will provide an opportunity for chronic, long-term research.

Statistical Analysis

Data collected will be analyzed using the successful and valid statistical approach to data gathered using single-patient crossover RCTs as described by Edgington (1975, 1984). Please refer to the outlined methods for more information.

Instruments and Materials

Medicinal Cannabis: Determination and Analysis

The research will focus on the use of two different strains of *cannabis sativa* with either higher cannabidiol (CBD) and lower delta-9-tetrahydrocannibinol (THC) content (defined, for purposes of this study, as ⩽15% CBD, ⩾2% THC) or high THC and low CBD content (⩽15% THC, ⩾2% CBD) with comparably similar terpene profiles (see Appendix A for terpene analysis information). The phytocannabinoid and terpene levels of the products will be assessed initially based on producer labels and then submitted to an independent laboratory for gas chromatographic analysis to ensure homogeneity and gain a more detailed report on the terpene profile in order to minimize discrepancies between the strains besides THC and CBD. Patients will be instructed to only use the cannabis that they have been provided with by the researchers for the duration of the study.

Administration Device

All participants will be provided with a Volcano vaporization device, the same as that found by the University of California Center for Medicinal Cannabis Research to be a "safe mode of delivery" (Abrams et. al, 2005). Patients will be instructed to only use this device to administer their medication, in order to minimize confounding variables presented by device contamination.

Screening Tools

This study will use screening tools that have demonstrated validity multiple times in clinical practice to determine changes in a patient's condition, with a preference for tools that have a higher sensitivity rather than specificity.

Global Assessment of Functioning (GAF):

The Global Assessment of Functioning is a subjective numeric scale which measures the adaptive functioning in a social, psychological and occupational capacity. It is scored along a scale of 0-100 with ten individual criteria determining which number correlates to how severely symptoms are affecting day to day functioning. The GAF has been determined to have high construct validity as a tool for patients with anxiety disorders (Schwartz, 2003).

Clinical Global Impression (CGI):

The CGI (Guy, 1976) is a 3-item observer rated scale intended to be completed by a physician that scores illness severity (CGI-S), global improvement or change (CGI-I) and therapeutic response. There is no global CGI score, each item is scored separately and gives a unique insight on how the patient's condition has changed. The CGI will be completed by an independent physician who is unaware of specific study conditions, in order to prevent bias.

PTSD Checklist - Military (PCL-M):

The PCL-M is a 17-item self-report measure which cross-references the experience of a patient with the DSM-IV diagnostic criteria for PTSD, focusing on responses to "stressful military experiences". For this study, responses will be concerning the past 30 days. For initial

inclusion in the trial, participants will be required to have a total initial symptom severity score of 42 - or in other words, they must meet the DSM-IV-TR diagnostic criteria of experiencing:

- At least one intrusion (re-experiencing) symptom;

- At least three avoidance (emotional numbing) symptoms;

- Two or more hyperarousal symptoms,

and indicate that they are distressed by each of these symptoms moderately (for example, by consistently answering 3 and occasionally 2 when asked how they are bothered by each experience; 1 - Not at All to 5 - Extremely). As advised by the U.S. Department of Veteran Affairs, patients will be considered responding to treatment with a change of 5 or more points, and this response will be considered clinically meaningful with a change of 10 or more points. Reports on the psychometric properties and validity of the PCL are strong, with Weathers reporting a Cronbach's Alpha consistency range of .97, and a sensitivity of 1.00 and specificity of 0.92 (meaning 100% of PTSD cases are detected and 8% may be detected incorrectly) reported by Blanchard (1996).

The Short Post-Traumatic Stress Disorder Rating Interview (SPRINT):

A brief assessment used to validate the diagnosis of PTSD. It consists of eight items that require subjects to rate the severity of the core symptoms of PTSD in the past week using a 4 point Likert scale. There are two other items that are related to overall improvement since the start of treatment. A study conducted by Connor and Davidson (2001) assessed the validity of the SPRINT against commonly used global stress scales as well as assessment scales specific to PTSD. The researchers found that the SPRINT was responsive to symptom change over time and was comparable to other measures of PTSD symptoms. The study also

found that the SPRINT had good test-retest reliability, internal consistency, convergent and divergent validity. A 96% accuracy rate for the diagnosis of PTSD was found with scores between 11 and 13. This will be conducted at the initial assessment, at the end of each treatment period and upon cessation of the study.

Intended Use of Results

Results of this research will be intended to be used for the goal of helping clinicians, primary care providers and patients determine the right type of medicinal cannabis they wish to employ in the treatment of PTSD. In regards to the modern medical community, medicinal marijuana is a novel treatment proposed for many ailments. With current findings suggesting a future for cannabis as a scientifically valid and efficacious treatment, the current method of "trial and error" with medication for those prescribed must be phased out. According to a systematic search of peer-reviewed journals on the PsycINFO, PubMed and Web of Science databases, there have been no studies examining the effects of different strains of *cannabis sativa* or *cannabis indica* raw plant material as classified by cannabinoid content on PTSD. Thus, our results will contribute a new area of understanding and possibilities for expansion in the academic pursuit of understanding medicinal cannabis. Ideally, our study will provide a template for other scientific inquiries approaching research on the effects of different cannabis strains and their cannabinoid profiles in the treatment of illness, who may utilize it, improve upon it, review its validity and perhaps attempt to reproduce our results. In comparison to studies examining the effects of either synthetic, individually extracted or paired cannabinoid preparations for the treatment of PTSD, these results will present those differences to the effect of treatment that a whole-plant preparation and an uncommonly supported route of administration brings to the discussion. These results should be incorporated into future research for the field. If the results of this study show that either high CBD, high THC or both forms of cannabis has resulted in a statistically significant improvement in patient condition, following-up with a well-thought out parallel group, double-blind, randomised

placebo-controlled study on the same topic, using the lessons gained from this study, will certainly be the next step.

Operation as a dispensary in conjunction with our offer to continue treatment will open up an oppurtunity for research on the long term effects of vaporized whole plant cannabis used medicinally.

Our research will provide results directly applicable to the medicinal marijuana program in Connecticut by only using cannabis manufactured and provided by licensed producer in the state of Connecticut. This will allow our research to provide scientific insight on the effects of specific cannabinoids when administered along with the entire spectrum of biologically active compounds present in cannabis, including terpenoids, all other phytocannabinoids and flavonoids. In the opinion of the researchers, the data available on the medicinal use of cannabis that examines differing effects of specific cannabinoids based on cannabinoid levels in raw plant material is limited and warrants further development. It seems most of the research has focused on specific cannabinoids using a delivery system which contains extracted and isolated cannabinoids in solvent. This approach certainly allows conclusions to be drawn accurately on one or a few cannabinoids, but does not provide adequate insight into the efficacy of those cannabinoids when administered in the form of cannabis products and cannot apply completely to the many patients who are using medicinal marijuana products. While it is frequently the case that the isolation and study of plant alkaloids produces more safe, potent and precise pharmaceutical compounds, we do not currently know enough about medicinal cannabis use to discredit the possibility that the unique combination of various pharmacologically relevant and biologically active compounds in cannabis may be more medically efficacious for certain patient populations in the treatment of debilitating medical

conditions. It would prove a more reasonable approach to examine the effects of the plant and then break it down into its constituent compounds, extract/isolate them and examine their individual effects, rather than the other way around. With the safety profile of cannabis, it may be more effective to gain insight into which compounds we may wish to combine based on research conducted using reliably HPLC analyzed whole-plant preparations. Once it is more understood how the myriad compounds present in the cannabis plant interact with each other and affect the body, there will be more information that may be used in the creation of combination cannabinoid medications that may be able to minimize side effects and treat symptoms with increased specificity.

According to a systematic search of peer-reviewed journals on the PsycINFO, PubMed and Web of Science databases, there have been no studies examining the effects of different strains of *cannabis sativa* or *cannabis indica* raw plant material as classified by cannabinoid content on PTSD. Thus, our results will contribute a new area of understanding and possibilities for expansion in the academic pursuit of understanding medicinal cannabis more fully. Ideally, our study will provide a template for other scientific inquiries approaching research on the effects of different cannabis strains and their cannabinoid profiles in the treatment of illness, who may utilize it, improve upon it, review its validity and perhaps attempt to reproduce our results. We also intend to incorporate our results into future research, which will be guided by our findings.

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